PCT/EP03/02365

10/508936

INVESTOR IN PEOPLE

The Patent Office
Concept House
Cardiff Road
Newport
South Wales
NP10 8QQ

REC'D 17 APR 2003
WIPO PCT

I, the undersigned, being an officer duly authorised in accordance with Section 74(1) and (4) of the Deregulation & Contracting Out Act 1994, to sign and issue certificates on behalf of the Comptroller-General, hereby certify that annexed hereto is a true copy of the documents as originally filed in connection with the patent application identified therein.

In accordance with the Patents (Companies Re-registration) Rules 1982, if a company named in this certificate and any accompanying documents has re-registered under the Companies Act 1980 with the same name as that with which it was registered immediately before re-registration save for the substitution as, or inclusion as, the last part of the name of the words "public limited company" or their equivalents in Welsh, references to the name of the company in this certificate and any accompanying documents shall be treated as references to the name with which it is so re-registered.

In accordance with the rules, the words "public limited company" may be replaced by p.l.c., plc, P.L.C. or PLC.

Re-registration under the Companies Act does not constitute a new legal entity but merely subjects the company to certain additional company law rules.

PRIORITY DOCUMENT
SUBMITTED OR TRANSMITTED IN
COMPLIANCE WITH
RULE 17.1(a) OR (b)

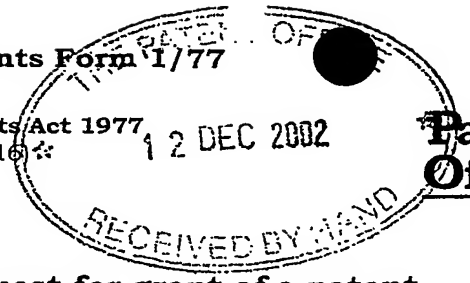
Signed P. Mahoney

Dated 24 January 2003

BEST AVAILABLE COPY

Patents Form 1/77

Patents Act 1977
(Rule 16)



The Patent Office

130EC0[redacted]0728-1 D00524
P01/7[redacted]00-0229054.2

1/77

Request for grant of a patent

(See the notes on the back of this form. You can also get an explanatory leaflet from the Patent Office to help you fill in this form)

The Patent Office
Cardiff Road
Newport
Gwent NP10 8QQ

1.	Your reference	4-32810P1
2.	Patent application number *(The Patent Office will fill in this part)*	0229054.2
3.	Full name, address and postcode of the or of each applicant *(underline all surnames)*	NOVARTIS AG LICHTSTRASSE 35 4056 BASEL SWITZERLAND
	Patent ADP number *(if you know it)*	
	If the applicant is a corporate body, give the country/state of its incorporation	SWITZERLAND 7125437005
4.	Title of invention	Organic compounds
5.	Name of your agent *(If you have one)*	
	"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*	B.A. YORKE & CO. CHARTERED PATENT AGENTS COOMB HOUSE, 7 ST. JOHN'S ROAD ISLEWORTH MIDDLESEX TW7 6NH
	Patents ADP number *(if you know it)*	1800001

6.	If you are declaring priority from one ore more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and *(if you know it)* the or each application number	Country	Priority application number *(if you know it)*	Date of filing (day/month/year)

7.	If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application	Number of earlier application	Date of filing (day/month/year)

8.	Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer 'Yes' if:* *a) any applicant named in part 3 is not an inventor, or* *b) there is an inventor who is not named as an applicant, or* *c) any named applicant is a corporate body.* *(see note (d))*	Yes

Patents Form 1/77

9. Enter the number of sheets for any of the following items you are filing with this form. Do not count copies of the same document

Continuation sheets of this form	
Description	28 DM
Claim(s)	6
Abstract	
Drawing(s)	

10. If you are also filing any of the following, state how many against each item.

Priority documents	
Translations of priority documents	
Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	
Request for preliminary examination and search *(Patents Form 9/77)*	One /
Request for substantive examination *(Patents Form 10/77)*	
Any other documents *(please specify)*	

11. I/We request the grant of a patent on the basis of this application

Signature: B.A. Yorke & Co

Date: 12 December 2002

12. Name and daytime telephone number of person to contact in the United Kingdom

Mrs. J. Crook
020 8560 5847

Warning

After an application for a patent has been filed. the Comptroller of the Patent Office will consider whether publication or communication of the invention should be prohibited or restricted under Section 22 of the Patents Act 1977. You will be informed if it is necessary to prohibit or restrict your invention in this way. Furthermore, if you live in the United Kingdom, Section 23 of the Patents Act 1977 stops you from applying for a patent abroad without first getting written permission from the Patent Office unless an application has been filed at least 6 weeks beforehand in the united Kingdom for a patent for the same invention and either no direction prohibiting publication or communication has been given, or any such direction has been revoked.

Notes

a) *If you need help to fill in this form or you have any questions, please contact the Patent Office on 0645 500505.*

b) *Write your answers in capital letters using black ink or you may type them.*

c) *If there is not enough space for all the relevant details on any part of this form, please continue on a separate sheet of paper and write "see continuation sheet" in the relevant part(s). Any continuation sheet should be attached to this form.*

d) *Once you have filled in the form you must remember to sign and date it.*

e) *For details of the fee and ways to pay please contact the Patent Office.*

Organic Compounds

This invention relates to organic compounds, in particular to pharmaceutical compositions for use in combination with cytotoxic therapy and Heat shock for the treatment of tumors.

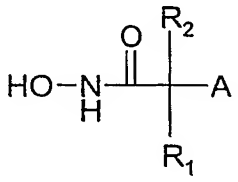
Carcinoma is by far the most common type of cancer it accounts for about 80% of all cases of cancer. The severity of a carcinoma can vary widely with pancreatic cancer being one of the most aggressive and lethal neoplasms with an extremely low 5-year survival rate; Landis, S. et al (CA Cancer J. Clin., *49*: 8-31, 1999) and Niederhuber, J. E. et al (Cancer, *76*:1671-1677, 1995). Because most patients with pancreatic cancer miss the opportunity for complete surgical resection at the time of diagnosis, radiotherapy remains as a major component of treatment modalities for controlling tumor progression. Malignant progression of pancreatic cancer depends not only on rapid proliferation of tumor cells but also on other biological behaviours including motility, invasiveness, and metastatic potential. More generally radiotherapy remains a major therapeutic option for patients with various other types of advanced cancer. Radiotherapy besides having the desired effect also has an effect on malignant biological behaviours for example it has now been found that while it significantly inhibits cell proliferation and migration irradiation may enhance the invasive potential in pancreatic cancer cells.

Current treatments for cancer are effective to some extent but all have some undesirable effects and carry risks which need to be taken into account when choosing a specific treatment. The side effects of some treatments also include the promotion of the cancer. A treatment that has all the benefits of the current treatments but without or with a reduced risk of promoting the development of the cancer would be highly beneficial.

We have now found that certain matrix metalloproteinase inhibitors are effective when used in combination with Heat shock and cytotoxic therapy for the treatment of tumors especially tumors of the brain, breast, larynx, pancreas, skin, tongue, uterine cervix also leukaemia and lymphoma.

Accordingly the invention provides a method of treating tumors in a subject in need of such treatment which comprises administering to the subject an effective amount of a matrix metalloproteinase inhibitor in combination with heat shock and acytotoxic therapy

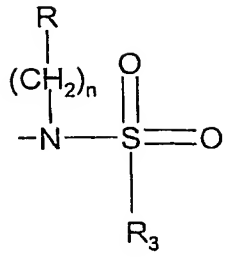
Preferably the invention provides a method of treating tumors in a subject in need of such treatment which comprises administering to the subject an effective amount of a hydroxamic acid derivativematrix metalloproteinase inhibitor (of the formula I) in combination with heat shock and acytotoxic therapy.
Hydroxamic acid derivative metalloproteinase inhibitors are well known in the art. A suitable metalloproteniase inhibitor for use in the method of the invention is, for instance, a compound of formula I



(I)

(i) Wherein

A represents substituent of formula II or III;



Formula II

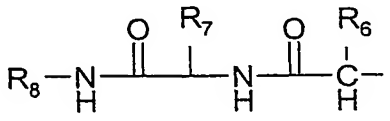
wherein

R represents hydrogen, lower alkyl, aryl-lower alkyl, aryl, mono- or poly-halo-lower alkyl, cycloalkyl, cycloalkyl-lower alkyl, (oxa or thia)-cycloalkyl, [(oxa or thia)-cycloalkyl]-lower alkyl, hydroxy-lower alkyl, acyloxy-lower alkyl, lower alkoxy-lower alkyl, lower alkyl-(thio, sulfinyl or sulfonyl)-lower alkyl, (amino, mono- or di-lower alkylamino)-lower alkyl, acylamino-lower alkyl, (N-lower alkyl-piperazino or N-aryl- lower alkylpiperazino)-lower alkyl, or (morpholino, thiomorpholino, piperidino, pyrrolidino, piperidyl or N-lower alkylpiperidyl)-lower alkyl;

R_3 represents aryl that may be unsubstituted or substituted by R_4 and R_5;

R_4 or R_5 represents independently hydrogen, lower alkyl, lower alkoxy, halogen, hydroxy, acyloxy, lower alkoxy-lower alkoxy, trifluromethyl or cyano, oxy-C_2-C_3-alkylene, 1- or 2-napthyl; or R_4 and R_5 together on adjacent carbon atoms represent lower alkylenedioxy;

n represents an integer from 1 to 5;



Formula III

Wherein

R_6 is C_{3-12} alkyl, C_{3-12} alkenyl, C_{3-7}(optionally hydroxy-, C_{1-6} alkoxy-, amino-, or C_{1-6} alkylamino- substituted) cycloalkyl, C_{5-14} aryl, or C_{5-14} aryl(C_{1-6} alkyl), wherein aryl groups are optionally substituted by hydroxy-, C_{1-6} alkyl-, C_{1-6} alkoxy-, amino-, halo- or cyano-;

R_7 is C_{1-10} (optionally hydroxy- or C_{1-6}alkoxy- amino-, C_{1-6} alkylamino-, thiol-, C_{1-6} alkylmercapto- or protected hydroxy-, amino- or thiol- substituted) alkyl, C_{6-14} (optionally hydroxy-, C_{6-14}aryloxy-, or C_{1-6}alkoxy-, amino-, C_{1-6} alkylamino-, halo-, or cyano-substituted)aryl, or indolylmethyl;

R_8 is methyl, pyridyl, or a substituent of formula X-Y- wherein X is morpholino, pyridyl or aryl, and Y is C_{1-12}alkylene in which up to four of the methylene (-CH_2-) units are optionally replaced with -CO-, -NH-, -SO_2- or -O-;

R_1 is hydrogen, lower alkyl, aryl, aryl-lower alkyl, mono- or poly-halo-lower alkyl, cycloalkyl, cycloalkyl-lower alkyl, cycloalkyl-cycloalkyl, aryl-lower alkyl-lower cycloalkyl, lower alkyl-cycloalkyl, lower alkoxy-lower alkyl-cycloalkyl, aryl-cycloalkyl, cycloalkyl-lower alkyl-cycloalkyl, halo-lower alkyl-cycloalkyl, hydroxy-lower alkyl, acyloxy-lower alkyl, lower alkoxy-lower alkyl, aryl-lower alkoxy-lower alkyl, lower alkyl-(thio, sulfinyl or sulfonyl)-lower alkyl, (amino, mono- or di-lower alkylamino)-lower alkyl, (N-lower alkyl-piperazino or N-aryl-lower alkylpiperazino)-lower alkyl, (morpholono, thiomorpholino, piperidino, pyrrolidino, piperidyl or N-lower alkylpiperidyl)-lower alkyl, acylamino-lower alkyl, piperidyl, N-lower alkylpiperidyl or a substituent of formula IV

$D-(O-(CR_9H)_z)_m-O-CH_2-$ Formula IV

wherein

z is 1, 2, 3 or 4;

m is 0, 1, 2 or 3;

each R_9 is independently H, C_{1-10} (optionally hydroxy-, C_{1-6} alkoxy-, amino-, C_{1-6} alkylamino-, thiol-, C_{1-6} alkylmercapto- or protected hydroxy, amino or thiol substituted) alkyl, C_{2-6} alkenyl, C_{6-14}(optionally hydroxy-, C_{1-6} alkoxy-, amino-, C_{1-6} alkylamino-, halo- or cyano-substituted) aryl, or C_{6-14} (aryl) C_{1-6}alkyl;

D is hydrogen, C_{1-10} alkyl, C_{6-14} aryl, C_{6-14} aryl(C_{1-6} alkyl), (C_{6-14} aryl)carbonyl, or (C_{1-10} alkyl)carbonyl;

R_2 is hydrogen or lower alkyl,

(ii) or wherein

R (of formula II under (a)) and R_1 together with the chain to which they are attached from a 1,2,3,4-tetrahydro-isoquinoline, piperidine, oxazolidine, thiazolidine or pyrrolidine ring, each unsubstituted or substituted by lower alkyl; and

R_3 and R_2 have meaning as defined under (i);

(iii) or wherein

R_1 and R_2 together with the carbon atom to which they are attached form a ring system selected from lower cycloalkane which is unsubstituted or substituted by lower alkyl' oxa-cyclohexane, thia-cyclohexane, indane, tetralin, piperidine or piperidine substituted on nitrogen by acyl, lower alkyl, aryl-lower alkyl, (carboxy, esterified or amidated carboxy)-lower alkyl or by lower alkylsulfonyl; and

R_3 and R meaning as defined under (i);

or a pharmaceutically acceptable prodrug derivative thereof; or a pharmaceutically acceptable salt thereof.

Further the invention provides the use of a hydroxamic acid derivative metalloproteinase inhibitor, for instance a compound of formula I (or pharmaceutically acceptable salt or prodrug ester thereof) for the preparation of a medicament for use in combination with heat shock and cytotoxic therapy in the treatment of tumors.

In a further aspect the invention provides use of a hydroxamic acid derivative metalloproteinase inhibitor, for instance a compound of formula I (or pharmaceutically acceptable salt or prodrug ester thereof) in combination with heat shock and cytotoxic therapy for the treatment of tumors.

In yet further aspect the invention provides a hydroxamic acid derivative matrix metalloproteinase inhibiting agent comprising, for instance a compound of formula I (or pharmaceutically acceptable salt or prodrug ester thereof) as active ingredient for use in combination with heat shock and cytotoxic therapy for the treatment of tumors which shows heat shock induced MMP expression especially MMP-3 expression.

In still yet further aspect the invention provides a package comprising a hydroxamic acid derivative metalloproteinase inhibitor, for instance a compound of formula I (or pharmaceutically acceptable salt or prodrug ester thereof) together with instructions for the use in combination with heat shock and cytotoxic therapy in the treatment of tumors.

The invention may be used for the treatment of any tumor which is susceptible to treatment by cytotoxic therapy, including the treatment of solid tumours, carcinoma, adenocarcinoma. For example the invention may be used in the treatment of tumors of the brain, breast, larynx, skin, tongue, uterine cervix and also leukaemia and lymphoma, especially pancreatic tumors.

Above and elsewhere in the present description the following terms have the meanings given below:

The term "lower" referred to above and hereinafter in connection with organic radicals or compounds respectively defines a compound or radical which may be branched or unbranched with up to and including 7, preferably up to and including 4 carbon atoms.

A lower alkyl group is branched or unbranched and contains 1 to 7 carbon atoms, preferably 1-4 carbon atoms. Lower alkyl represents, for example, methyl, ethyl, propyl, butyl, isopropyl or isobutyl.

A lower alkoxy (or alkyloxy) group preferably contains 1-7 carbon atoms, advantageously 1-6 carbon atoms, and represents for example methoxy, ethoxy, propoxy, isopropoxy, isobutoxy, preferably methoxy. Lower alkoxy includes cycloalkyloxy and cycloalkyl-lower alkyloxy.

Halogen (halo) preferably represents chloro or fluoro but may also be bromo or iodo.

Aryl represents carbocyclic or heterocyclic aryl including biaryl.

Carbocyclic aryl represents monocyclic, bicyclic or tricyclic aryl, for example phenyl or phenyl mono-, di- or tri-substituted by one, two or three radicals selected from

lower alkyl, lower alkoxy, hydroxy, halogen, cyano, trifluoromethyl, lower alkylenedioxy, and oxy-C2-C3-alkylene; or 1- or 2-naphthyl. Lower lkylene is a divalent substituent attached to two adjacent carbon atoms of phenyl, e.g. methylenedioxy or ethylenedioxy. Oxy-C2-C3-alkylene is also a divalent substituent attached to two adjacent carbon atoms pf phenyl, e.g. oxyethylene or oxypropylene, An example for oxy-C2-C3-alkylene-phenyl is 2,3-dihydrobenzofuran-5-yl.

Heterocyclic aryl represents monocyclic or bicyclic heteroaryl, for example pyridyl, indolyl, quinoxalinyl, quinolyl, isoquinolyl, benzothienyl, benzofuranyl, benzopyranyl, benzothiopyranyl, furanyl, pyrrolyl, thiazolyl, oxazolyl, isoxazolyl, triazolyl, tetrazolyl, pyrazolyl, imidazolyl, thienyl, or any said radical substituted, especially mono- or di-substituted, by lower alkyl or halogen. Pyridyl represents 2-, 3- or 4-pyridyl, advantageously 2- or 3-pyridyl. Thienyl represents 2- or 3-thienyl, advantageously 2-thienyl. Quinolyl represents 2-, 3- or 4-quinolyl, advantageously 2-quinolyl. Isoquinolyl represents preferably 1-, 3- or 4-isoquinolyl. Benzopyranyl, benzothiopyranyl represent preferably 3-benzopyranyl or 3-benzothiopyranyl, respectively. Thiazolyl represents preferably 2- or 4-thiazolyl, advantageously 4-thiazolyl. Triazolyl is preferably 1-, 2- or 5-(1,2,4-triazolyl). Tetrazolyl is preferably 5-tetrazolyl. Imidazolyl is preferably 4-imidazolyl.

Biaryl is preferably carbocyclic biaryl, e.g biphenyl, namely 2, 3 or 4-biphenyl, advantageously 4-biphenyl, each optionally substituted by e.g. lower alkyl, lower alkoxy, halogen, trifluoromethyl or cyano.

Cycloalkyl represents a saturated cyclic hydrocarbon optionally substituted by lower alkyl which contains 3 to 8 ring carbons and is advantageously cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl optionally substituted as hereinbefore defined; cycloalkyl includes heterocyclyl.

Heterocyclyl represents a saturated cyclic hydrocarbon containing one or more, preferably 1 or 2, hetero atoms selected from O, N or S, and preferably from 3 to 10, more preferably 5 to 8, ring atoms; for example, tetrahydrofuranyl, tetrahydrothienyl,

tetrahydropyrrolyl, piperidinyl, piperazinyl or morpholino; all of which may be optionally substituted, for instance as hereinbefore defined.

Amino may be optionally substituted, e.g. by lower alkyl.

Aryl-lower alkyl represents preferably (carbocyclic aryl or heterocylic aryl)-lower alkyl.

Carbocyclic aryl-lower alkyl preferably represents aryl-straight chain or -branched C_{1-4}-alkyl in which carbocyclic aryl has meaning as defined above, e.g. benzyl or phenyl-(ethyl, propyl or butyl), each unsubstituted or substituted preferably on the phenyl ring as hereinbefore defined for carbocyclic aryl above.

Heterocyclic aryl-lower alkyl represents preferably straight chain or branched heterocyclic aryl-C_{1-7}-alkyl in which heterocyclic aryl has meaning as defined above.

Cycloalkyl-lower alkyl represents e.g. (cyclopropyl- or cyclobutyl)-(methyl or ethyl).

Combination refers to every combination, of a MMP inhibitor of formula I, heat shock and cytotoxic therapy, such that there is an effect which would not be obtained if the MMP inhibitor of formula I is administered without prior, simultaneous or subsequent heat shock or cytotoxic therapy. Wherein heat shock and cytotoxic therapy can be continuous, sequential or sporadic. Or an effect which would not be obtained if there is cytotoxic therapy without prior, simultaneous or subsequent heat shock or administration of a MMP inhibitor of formula I. Wherein heat shock or administration of MMP inhibitor of formula I can be continuous, sequential or sporadic

Preferably combination refers to every combination, of a MMP inhibitor of formula I, heat shock and cytotoxic therapy, such that there is an effect on MMP expression or invasion potential which would not be obtained if

a) The MMP inhibitor is administered without prior, simultaneous or subsequent heat shock and prior, simultaneous or subsequent cytotoxic therapy. Wherein heat shock and cytotoxic therapy can be continuous, sequential or sporadic and Wherein cytotoxic therapy can be continuous, sequential or sporadic;

b) There is cytotoxic therapy without prior, simultaneous or subsequent administration of heat shock and without prior, simultaneous or subsequent administration of a MMP inhibitor. Wherein administration of heat shock and MMP inhibitor can be continuous, sequential or sporadic.

c) There is heat shock without prior, simultaneous or subsequent cytotoxic therapy and without prior, simultaneous or subsequent administration of a matrix metalloproteinase inhibitor and wherein administration of heat shock and matrix metalloproteinase inhibitor can be independently continuous, sequential or sporadic and

Cytotoxic therapy refers to a therapy or combination of therapies which causes cell damage or death. For example those therapies which are known for treating cancer for example Biological therapy (e.g. Interferon, Interlukin-2), Chemotherapy, Chemotherapy drugs (e.g Actinomycin D, Adriamycin, Altretamine, Asparaginase, Bleomycin, Busulphan, Capecitabine, Carboplatin, Carmustine, Chlorambucil, Cisplatin, Cyclophosphamide, Cytarabine, Dacarbazine, Daunorubicin, Doxorubicin, Epirubicin, Etoposide, Fludarabine, Fluorouracil, Gemcitabine, Hydroxyurea, Idarubicin, Ifosfamide, Irinotecan, Liposomal Doxorubicin, Lomustine, Melphalan, Mercaptopurine, Methotrexate, Mitomycin, Mitozantrone, Oxaliplatin, Procarbazine, Steroids, Streptozocin, Taxol, Taxotere, Taxotere - the TACT trial, Tamozolomide, Thioguanine, Thiotepa, Tomudex, Topotecan, Treosulfan, UFT (Uracil-tegafur), Vinblastine, Vincristine,Vindesine, Vinorelbine), Combination chemotherapy regimes (e.g. Mayo regime, de Gramont regime, Irinotecan with de Gramont regime, ECF regime, ECF

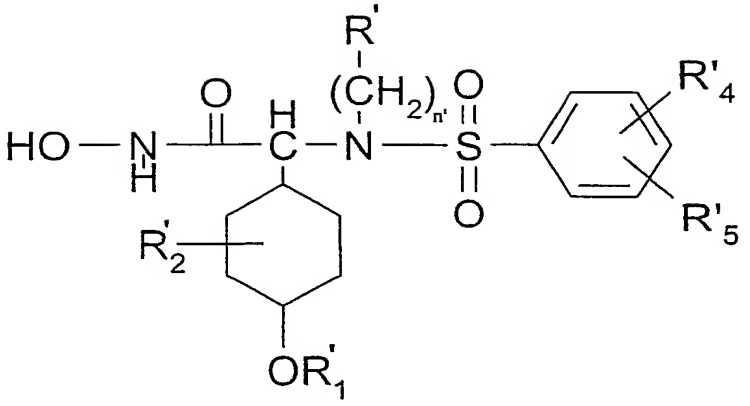
regime, Paclitaxel (Taxol) and Carboplatin, CHOP regime, AC regime, CMF regime, EC regime, MM regime, MMM regime, ECF regime), monoclonal antibodies (e.g. Rituximab, Tositumomab, Tratuxumab), Imatinib, photodynamic therapy, radiotherapy. Preferably cytotoxic therapy refers to radiotherapy.

Heat shock refers to any method of causing a heat shock response by a cell or cells in a tumor or within the area of a tumor. Heat shock may be administered to the whole body, part of the body or locally to the tumor and may be caused by external or internal means, for example heating rods, microwaves, radiofrequences, ultrasound, thermal blankets, thermal baths, lasers, inducing fever e.g administration of a pyrogen, etc.

The term "tumor" is intended to mean malignant tumors and benign tumors in particular cancerous tumors for example cancers of the brain, breast, larynx, pancreas, skin, tongue, uterine cervix also leukaemia and lymphoma.

Preferred embodiments provide a method of treating tumor which can be treated with cytotoxic therapy in a subject in need of such treatment which comprises cytotoxic therapy and heat shock in combination with administering to the subject an effective amount of ;

a) Compound of formula V



(V)

wherein

R' represents aryl;

R'_1 represents lower alkyl, cycloalkyl, aryl-lower alkyl, lower alkoxy-lower alkyl, aryl, cycloalkyl-lower alkyl or halogen-lower alkyl;

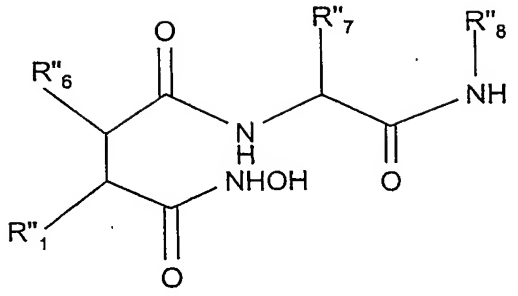
R'_2 represents hydrogen or lower alkyl;

R'_4 and R'_5 represent independently hydrogen, lower alkyl, lower alkoxy, halogen, hydroxy, acyloxy, lower alkoxy-lower alkoxy, trifluoromethyl or cyano; or R'_4 and R'_5 together on adjacent carbon atoms represent lower alkylenedioxy;

n' represents an integer from 1 to 5;

or a pharmaceutically acceptable prodrug derivative thereof; or a pharmaceutically acceptable salt thereof.

b) Compound of formula VI



(VI)

wherein

$\mathbf{R"_1}$ is a substituent of Formula IV":

$$D"\text{-}(O\text{-}(CR"_9H)_{z"})_{m"}\text{-}O\text{-}CH_2\text{-} \qquad \text{Formula IV"}$$

wherein

z" is 1, 2, 3 or 4, preferably 2;

m" is 0, 1, 2 or 3;

each $\mathbf{R"_9}$ is

independently H, $C_{1\text{-}10}$ (optionally hydroxy-, $C_{1\text{-}6}$ alkoxy-, amino-, $C_{1\text{-}6}$ alkylamino-, thiol-, $C_{1\text{-}6}$ alkylmercapto- or protected hydroxy, amino or thiol substituted) alkyl, $C_{2\text{-}6}$ alkenyl, $C_{6\text{-}14}$(optionally hydroxy-, $C_{1\text{-}6}$ alkoxy-, amino-, $C_{1\text{-}6}$ alkylamino-, halo- or cyano-substituted) aryl, or $C_{6\text{-}14}$ (aryl) $C_{1\text{-}6}$alkyl; preferably H, phenyl, benzyl or $C_{1\text{-}5}$ alkyl;

D" is hydrogen, C_{1-10} alkyl, C_{6-14} aryl, C_{6-14} aryl(C_{1-6} alkyl), (C_{6-14} aryl)carbonyl, or (C_{1-10} alkyl)carbonyl; preferably hydrogen, C_{1-6} alkyl (e.g., methyl or cyclohexyl), phenyl or benzyl;

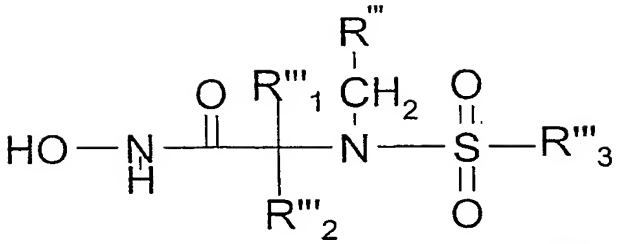
R"$_6$ is C_{3-12} alkyl, C_{3-12} alkenyl, C_{3-7}(optionally hydroxy-, C_{1-6} alkoxy-, amino-, or C_{1-6} alkylamino- substituted) cycloalkyl, C_{5-14} aryl, or C_{5-14} aryl(C_{1-6} alkyl), wherein aryl groups are optionally substituted by hydroxy-, C_{1-6} alkyl-, C_{1-6} alkoxy-, amino-, halo- or cyano-; preferably phenyl, 4-methylphenyl, cyclohexyl or isobutyl;

R"$_7$ is C_{1-10} (optionally hydroxy- or C_{1-6}alkoxy- amino-, C_{1-6} alkylamino-, thiol-, C_{1-6} alkylmercapto- or protected hydroxy-, amino- or thiol- substituted) alkyl (e.g., *t*-butyl. or cyclohexylmethyl), C_{6-14} (optionally hydroxy-, C_{6-14}aryloxy-, or C_{1-6}alkoxy-, amino-, C_{1-6} alkylamino-, halo-, or cyano- substituted) aryl (e.g., benzyl, *p*-methoxybenzyl, *p*-benzyloxybenzyl), or indolylmethyl (e.g., 2-indolylmethyl); preferably benzyl or *t*-butyl;

R"$_8$ is methyl, pyridyl, or a substituent of formula X"-Y"- wherein X" is morpholino, pyridyl or aryl (preferably morpholino), and Y" is C_{1-12}alkylene in which up to four of the methylene (-CH_2-) units are optionally replaced with -CO-, -NH-, -SO_2- or -O-; for example methyl, 2-pyridyl, morpholinocarbonylmethyl, 5-(morpholino)pentyl, or 5-(morpholinocarbonyl)pentyl;

or a pharmaceutically acceptable prodrug derivative thereof; or a pharmaceutically acceptable salt thereof.

c) Compound of formula VII



(VII)

(i') wherein

R"' represents hydrogen, lower alkyl, aryl-lower alkyl, aryl, mono- or poly-halo-lower alkyl, cycloalkyl, cycloalkyl-lower alkyl, (oxa or thia)-cycloalkyl, [(oxa or thia)-cycloalkyl]-lower alkyl, hydroxy-lower alkyl, acyloxy-lower alkyl, lower alkoxy-lower alkyl, lower alkyl-(thio, sulfinyl or sulfonyl)-lower alkyl, (amino, mono- or di-lower alkylamino)-lower alkyl, acylamino-lower alkyl, (N-lower alkyl-piperazino or N-aryl-lower alkylpiperazino)-lower alkyl, or (morpholino, thiomorpholino, piperidino, pyrrolidino, piperidyl or N-lower alkylpiperidyl)-lower alkyl;

R'''_1 is hydrogen, lower alkyl, aryl, aryl-lower alkyl, mono- or poly-halo-lower alkyl, cycloalkyl, cycloalkyl-lower alkyl, hydroxy-lower alkyl, acyloxy-lower alkyl, lower alkoxy-lower alkyl, aryl-lower alkoxy-lower alkyl, lower alkyl-(thio, sulfinyl or sulfonyl)-lower alkyl, (amino, mono- or di-lower alkylamino)-lower alkyl, (N-lower alkyl-piperazino or N-aryl-lower alkylpiperazino)-lower alkyl, (morpholono, thiomorpholino, piperidino, pyrrolidino, piperidyl or N-lower alkylpiperidyl)-lower alkyl, acylamino-lower alkyl, piperidyl or N-lower alkylpiperidyl

R'''_2 is hydrogen or lower alkyl,

R'''_3 represents aryl which may be unsubstituted or substituted by R'''_4 and R'''_5;

R_4 or R_5 represents independently hydrogen, lower alkyl, lower alkoxy, halogen, hydroxy, acyloxy, lower alkoxy-lower alkoxy, trifluromethyl or cyano, oxy-C2-C3-alkylene, 1- or 2-napthyl; or R_4 and R_5 together on adjacent carbon atoms represent lower alkylenedioxy;

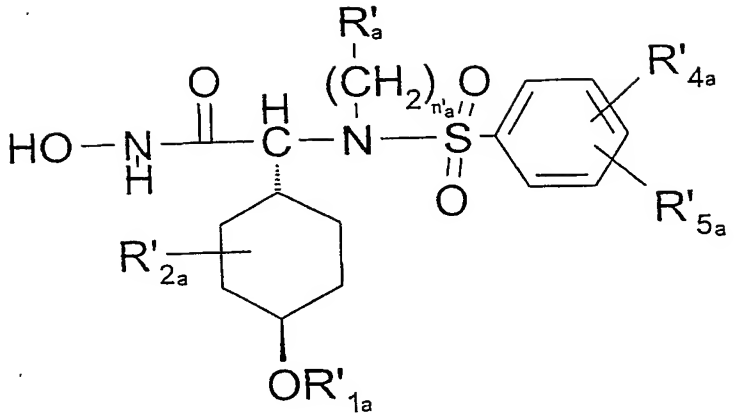
(ii') or wherein
R"' and $R"'_1$ together with the chain to which they are attached from a 1,2,3,4-tetrahydro-isoquinoline, piperidine, oxazolidine, thiazolidine or pyrrolidine ring, each unsubstituted or substituted by lower alkyl; and $R"'_2$ and $R"'_3$ have meaning as defined under (a);

(iii') or wherein
$R"'_1$ and $R"'_2$ together with the carbon atom to which they are attached form a ring system selected from lowercycloalkane which is unsubstituted or substituted by lower alkyl' oxa-cyclohexane, thia-cyclohexane, indane, tetralin, piperidine or piperidine substituted on nitrogen by acyl, lower alkyl, aryl-lower alkyl, (carboxy, esterified or amidated carboxy)-lower alkyl or by lower alkylsulfonyl; and $R'"_3$ and R'" meaning as defined under (a);

or a pharmaceutically acceptable prodrug derivative thereof; or a pharmaceutically acceptable salt thereof.

Particularly preferred embodiments provide a method of treating cancer which can be treated with radiotherapy in a subject in need of such treatment which comprises radiotherapy and or heat shock in combination with administering to the subject an effective amount of;

a') Compound of formula V having the trans configuration with respect to the 1,4-substituents on the cyclohexane ring, particularly those of formula V'



(V')

wherein

R'_a represents aryl;

R'_{1a} represents lower alkyl, cycloalkyl, aryl-lower alkyl or lower alkoxy-lower alkyl;

R'_{2a} represents hydrogen or lower alkyl;

R'_{4a} is hydrogen, lower alkoxy or halogen;

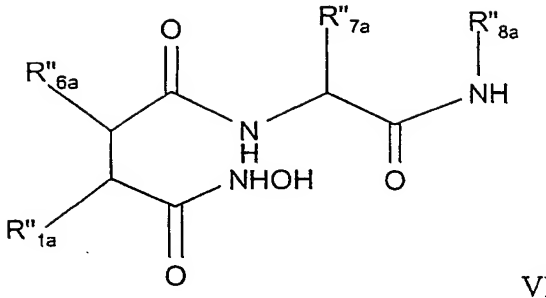
R'_{5a} is hydrogen or lower alkoxy; or

R'_{4a} and R'_{5a} together on adjacent carbon atoms represent methylenedioxy; and

n'_a is 1-4;

or a pharmaceutically acceptable prodrug derivative thereof; or a pharmaceutically acceptable salt thereof.

b') Compound of Formula VI'



VI'

wherein;

(i) $R"_{1a}$ is of formula IV"' or IV"" (preferably formula IV"')

$D"-(O-(CH_2)_{z"})_{m"}-O-CH_2-$ Formula IV"'

wherein D", z" and m" are as defined above.

$D"-O-(CHR"_9-(CH_2)_{z"})_{m"'}-O-CH_2-$ Formula IV""

wherein D", z" and $R"_9$ are as defined above and m"' is 0, 1 or 2.

or D" of formula IV"' is hydrogen, C_{1-6} alkyl, e.g., methyl or cyclohexyl (e.g., so that $R"_{1a}$ of formula VI' is for example hydroxymethyl, cyclohexyloxyethoxymethyl, methoxyethoxyethoxymethyl, or hydroxyethyloxymethyl) or (C_{6-14} aryl)carbonyl, e.g. benzoyl (e.g. so that $R"_1$ of formula VI is for example benzoyloxymethyl, benzoyloxyethoxyethyl or benzoyloxyethoxyethoxymethyl);

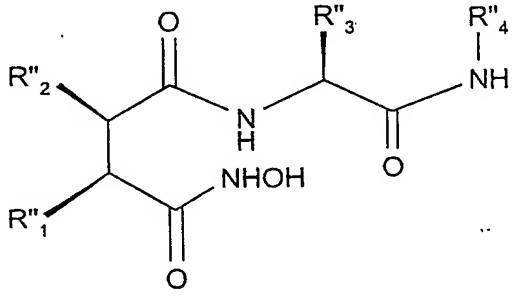
(ii) $R"_{6a}$ of formula VI' is cyclohexyl, phenyl, 4-methylphenyl or isobutyl;

(iii) $R"_{7a}$ of formula VI' is benzyl or *t*-butyl; and

(iv) R''_{8a} of formula VI' is methyl or morpholinocarbonyl(C_{1-6})alkyl.

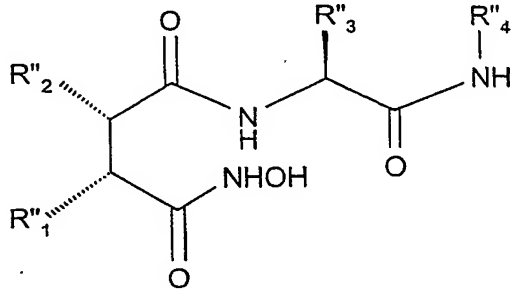
or a pharmaceutically acceptable prodrug derivative thereof; or a pharmaceutically acceptable salt thereof.

The configuration of the Novel Compounds of formula VI' is preferably that of Formula VIa:



VIa

or of Formula VIb:

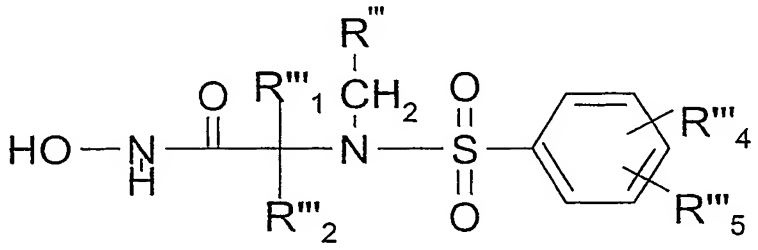


VIb

most preferably that of Formula VIa.

or a pharmaceutically acceptable prodrug derivative thereof; or a pharmaceutically acceptable salt thereof.

c') Compound of formula VII having R_3 represent phenyl which may be unsubstituted or substituted by R'''_4 and R'''_5 herein before defined, particularly those of the formula VII':



(VII')

wherein

R''' represents hydrogen, lower alkyl, aryl-lower alkyl, aryl, mono- or poly-halo-lower alkyl, cycloalkyl, cycloalkyl-lower alkyl, (oxa or thia)-cycloalkyl, [(oxa or thia)-cycloalkyl]-lower alkyl, hydroxy-lower alkyl, acyloxy-lower alkyl, lower alkoxy-lower alkyl, lower alkyl-(thio, sulfinyl or sulfonyl)-lower alkyl, (amino, mono- or di-lower alkylamino)-lower alkyl, acylamino-lower alkyl, (N-lower alkyl-piperazino or N-aryl-lower alkylpiperazino)-lower alkyl, or (morpholino, thiomorpholino, piperidino, pyrrolidino, piperidyl or N-lower alkylpiperidyl)-lower alkyl;

R'''_1 is hydrogen, lower alkyl, aryl, aryl-lower alkyl, mono- or poly-halo-lower alkyl, cycloalkyl, cycloalkyl-lower alkyl, hydroxy-lower alkyl, acyloxy-lower alkyl, lower alkoxy-lower alkyl, lower alkoxy-lower alkyl, lower alkyl-(thio, sulfinyl or sulfonyl)-lower alkyl, (amino, mono- or di-lower alkylamino)-lower alkyl, (N-lower alkyl-piperazino or N-aryl-lower alkylpiperazino)-lower alkyl, (morpholino, thiomorpholino,

piperidino, pyrrolidino, piperidyl or N-lower alkylpiperidyl)-lower alkyl, piperidyl, N-lower alkylpiperidyl or acylamino-lower alkyl represented by R'''$_{10}$-CONH-lower alkyl;

R'''$_2$ is hydrogen;

R'''$_{10}$ in R'''$_{10}$-CONH-lower alkyl is lower alkyl, aryl, di-lower alkylamino, N-lower alkylpiperazino, morpholino, thiomorpholino, piperidino, pyrrolidino, N-alkylpiperidyl, or (di-lower alkylamino, N-lower alkylpiperazino, morpholino, thiomorpholino, piperidino, pyrrolidino, pyridyl or N-lower alkylpiperidyl)- lower alkyl;

R'''$_4$ is hydrogen, lower alkoxy, hydroxy, aryl-lower alkoxy, lower alkylthio or aryl-lower alkylthio, lower alkyloxy-lower alkoxy, halogen, trifluoromethyl, lower alkyl, nitro or cyano;

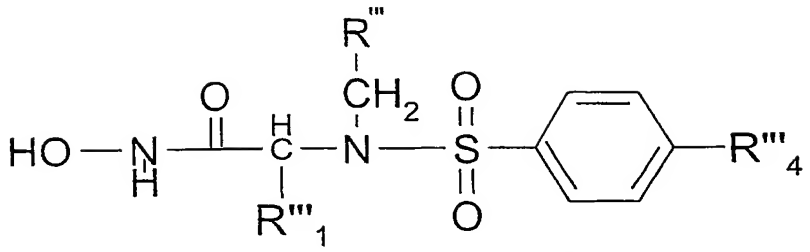
R'''$_5$ is hydrogen, lower alkyl or halogen;

or R'''$_4$ and R'''$_5$ together on adjacent carbon atoms represent methylenedioxy, ethylenedioxy, oxyethylene or oxypropylene;

or a pharmaceutically acceptable prodrug derivative thereof; or a pharmaceutically acceptable salt thereof.

further and most preferred embodiments provide a method of treating tumor in a subject in need of such treatment which comprises administering to the subject an effective amount of a pharmaceutical composition for use in combination with heat shock and cytotoxic therapy. Wherein said pharmaceutical composition is;

a") compound of formula VII"



(VII")

Where in;

R"' represents lower alkyl, aryl. trifluromethyl, cycloalkyl, (oxa or thia)-cycloalkyl;

R"'$_1$ is hydrogen, lower alkyl, aryl, aryl-lower alkyl, lower alkoxy-lower alkyl, lower alkyl-(thio, sulfinyl or sulfonyl)-lower alkyl, di-lower alkylamino-lower alkyl, (N-lower alkyl-piperazino, morpholino, thiomorpholino, piperidino, pyrrolidino)-lower alkyl or R"'$_{10}$-CONH-lower alkyl;

R"'$_{10}$ in R"'$_{10}$-CONH-lower alkyl is lower alkyl, aryl, di-lower alkylamino, N-lower alkylpiperazino, morpholino, thiomorpholino, piperidino, pyrrolidino, N-alkylpiperidyl, or (di-lower alkylamino, N-lower alkylpiperazino, morpholino, thiomorpholino, piperidino, pyrrolidino or N-lower alkylpiperidyl)- lower alkyl;

R"'$_4$ is hydrogen, lower alkoxy, aryl-lower alkoxy;

or a pharmaceutically acceptable prodrug derivative thereof; or a pharmaceutically acceptable salt thereof.

b") Compound of formula I, V, VI, VII, V', VI', VII', VIa, Vib or VII' that is a matrix metalloproteinase inhibitor.

c") one of the compounds disclosed in published international patent applications Nos. WO 98/14424, WO 97/22587 and EP 606046 in particular the compound N-hydroxy-2(R)-[[4-methoxyphenylsulfonyl](3-picolyl) amino] -3-methyl –butaneamide hydrochloride) monohydrate;
or a pharmaceutically acceptable prodrug derivative thereof, or a pharmaceutically acceptable salt thereof.

Compounds of formula I, II, III, IV, V, VI an VII and their synthesis are described in published international patent applications Nos. WO 98/14424, WO 97/22587 and EP 606046, the teachings of which are incorporated herein by reference.

The agents of the invention, i.e. the MMP inhibitors of formula I and pharmaceutically acceptable salts and prodrug derivatives, are preferably used in the form of pharmaceutical preparations that contain the relevant therapeutically effective amount of active ingredient optionally together with or in admixture with inorganic or organic, solid or liquid, pharmaceutically acceptable carriers which are suitable for administration.

The MMP inhibitor pharmaceutical compositions may be, for example, compositions for enteral, such as oral, rectal, aerosol inhalation or nasal administration, compositions for parenteral, such as intravenous or subcutaneous administration, or compositions for transdermal administration (e.g. passive or iontophoretic), or compositions for topical administration,

Preferably, the MMP inhibitor pharmaceutical compositions are adapted to oral administration.

The particular mode of administration and the dosage may be selected by the attending physician taking into account the particulars of the patient, especially age, weight, life style, activity level, etc.

The dosage of the Agents of the invention may depend on various factors, such as effectiveness and duration of action of the active ingredient, mode of administration, and/or sex, age, weight and individual condition of the subject to be treated.

The agents of the invention are useful in the manufacture of pharmaceutical compositions comprising an effective amount thereof in conjunction or admixture with excipients or carriers suitable for either enteral or parenteral application. In addition, they may also contain other therapeutically valuable substances. Said compositions are prepared according to conventional mixing, granulating or coating methods, respectively, and contain about 0.1 to 75%, preferably about 1 to 50%, of the active ingredient.

Parenteral formulations are especially injectable fluids that are effective in various manners, such as intravenously, intramuscularly, intraperitoneally, intranasally, intradermally or subcutaneously. Such fluids are preferably aqueous isotonic solutions or suspensions that can be prepared before use, for example from lyophilised preparations that contain the active ingredient alone or together with a pharmaceutically acceptable carrier. The pharmaceutical preparations be sterilised and/or contain adjuncts, for example preservatives, stabilisers, wetting agents and/or emulsifiers, solubilisers, salts for regulating the osmotic pressure and/or buffers.

Suitable oral forms are tablets and gelatin capsules comprising the active ingredient together with a) diluents, e.g. lactose, dextrose, sucrose, mannitol, sorbitol, cellulose and/or glycine; b) lubricants, e.g. silica, talcum, stearic acid, its magnesium or calcium salt and/or polyethyleneglycol; for tablets also c) binders e.g. magnesium aluminium

silicate, starch paste, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose and or polyvinylpyrrolidone; if desired d) disintegrants, e.g. starches, agar, alginic acid, or it's sodium salt, or effervescent mixtures; and/or e) adsorbents, colorants, flavours and sweeteners. Tablets may be either film coated or enteric coated according to methods known in the art.

Suitable formulations for transdermal application include an effective amount of a compound of the invention with carrier. Advantageous carriers include absorbable pharmacologically acceptable solvents to assist passage through the skin of the host. For example, transdermal devices are in the form of a bandage comprising a backing member, a reservoir containing the compound optionally with carriers, optionally a rate controlling barrier to deliver the compound to the skin of the host at a controlled and predetermined rate over a prolonged period of time, and means to secure the device to the skin.

Suitable formulations for topical application, e.g. to the skin and eyes, include aqueous solutions, suspensions, ointments, creams, gels, or sprayable formulations, for example, for delivery by aerosol or the like. Such topical formulations typically contain from about 0.1 up to about 50% by weight, preferably from about 1 up to about 20% by weight, of MMP inhibitor.

The following examples are intended to illustrate the invention and are not to be construed as being limitations thereon.

Examples

Example 1

Tablets each containing 50mg of N-hydroxy-2 (R)-[[4-methoxyphenylsulfonyl](3-picolyl)-amino]-3-methylbutanamide hydrochloride can be prepared as follows:

Composition (10,000 tablets)

Active ingredient	500.0g
Lactose	500.0g
Potato starch	325.0g
Gelatin	8.0g
Talc	60.0g
Magnesium stearate	10.0g
Silicon dioxide (finely divided)	20.0g
Ethanol	q.s

The active ingredient is mixed with the lactose and 292g of potato starch, and the mixture is moistened with an ethanolic solution of the gelatin and granulated through a sieve. After the granules have dried, the remainder of the potato starch, the magnesium stearate and the silicon dioxide are admixed and the mixture compressed to give tablets each weighing 145.0mg and containing 50.0mg of active ingredient, which can, if desired, be provided with breaking grooves to enable the dosage to be more freely adjusted.

Example 2

Preparation of 3000 capsules each containing 25mg of the active ingredient, for example, N-hydroxy-2 (R)-[[4-methoxyphenylsulfonyl](3-picolyl)-amino]-3-methylbutanamide hydrochloride:

Active ingredient	75.0g
Lactose	750.0g
Avicel PH 102 (microcrystalline cellulose)	325.0
Polyplasdone XL (polyvinylpyrrolidone)	30.0g
Purified water	q.s
Magnesium stearate	9.0g

The active ingredient is passed through a No. 30 hand screen.
The active ingredient, lactose, Avicel PH 102 and Polyplasdone XL are blended for 15 minutes in a mixer. The blend is granulated with sufficient water (about 500mL), dried in an oven at 35°C overnight, and passed through a No. 20 screen.

Magnesium stearate is padded through a No. 20 screen, added to the granulation mixture, and the mixture is blended for 5 minutes in a mixer. The blend is encapsulated in No. 0 hard gelatin capsules each containing and amount of the blend equivalent to 25mg of the active ingredient.

Example 3

Acquisition of array data

For gene expression analysis, HeLa cells seeded in 100mm petri dish are dipped in a water bath for 1 h at 44℃(±0.03℃). RNA is isolated from cells 0, 3, 6 and 12 h after heating. The cells just before heat shock treatment are used as control. Labeled probe is hybridized to a Human 1 cDNA microarray (no.G4100A; Agilent Technologies). The gene expression experiment is repeated two times.

Data analysis

Signal intensities of Cy3 and Cy5 from the 12,814 spots are quantified and analyzed by GenePix (Axon Instruments, Foster City, CA). Previously fagged spots by GenePix and 60% of spot pixels with intensities more than one standard deviation above the background pixel intensity are excluded. Residual spot signals are normalized so that median of all signal ratio (Cy3/Cy5) is 1.0. Then extract the genes that showed Cy3/Cy5 signal ratio > 2.0 or 0.5 < at both two times experiment.

Results

Analysis of gene expression profiles from data preprocessing

752 genes are up or down-regulated after heat shock. The temporal pattern of expression for 752 genes is more easily recognized through clustering. Using Fuzzy ART, those genes are separated into 8 clusters. Up-regulated genes at 0h play an important role in repair of injured cells. "Cluster 1" and "Cluster 2", containing 53 genes are selected and "Cluster 2" included HSP70 which is well known as heat shock response gene. Among these genes, focus on Matrix metalloproteinase 3 (MMP-3), which is included in "Cluster 2" and conduct next experiment.

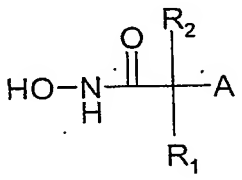
Inhibitory effect using MMP-3 inhibitor

MMP-3 inhibitor (no. 444225; CALBIOCHEM) is dissolved in DMSO. The final concentration of MMP-3 Inhibitor in each culture medium is 13μM. With the same concentration DMSO is used as control. MMP-3 inhibitor is added 1h before heat shock and dishes are dipped in water bath at 44℃ for 60, 75 and 90 min to make the surviving curve. Surviving cells are counted by trypan blue dye exclusion method after 3 days. MMP-3 Inhibitor induced much more cell death than DMSO. These data indicates that MMP-3 appears to play an important role in restoration of injured cells, and thus inhibition of MMP-3 should inhibit recovery of injured cells.

Claims

1. A method of treating cancer in a subject in need of such treatment which comprises cytotoxic therapy in combination with heat shock and administering to the subject an effective amount of a matrix metalloproteinase.

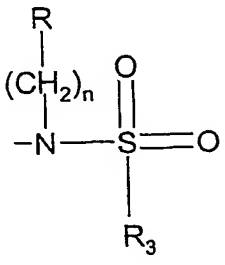
2. A method of treating cancer in a subject in need of such treatment which comprises cytotoxic therapy in combination with heat shock and administering to the subject an effective amount of a matrix metalloproteinase inhibitor of the formula I



(I)

(i) Wherein

A represents substituent of formula II or III;



Formula II

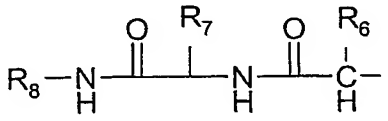
wherein

R represents hydrogen, lower alkyl, aryl-lower alkyl, aryl, mono- or poly-halo-lower alkyl, cycloalkyl, cycloalkyl-lower alkyl, (oxa or thia)-cycloalkyl, [(oxa or thia)-cycloalkyl]-lower alkyl, hydroxy-lower alkyl, acyloxy-lower alkyl, lower alkoxy-lower alkyl, lower alkyl-(thio, sulfinyl or sulfonyl)-lower alkyl, (amino, mono- or di-lower alkylamino)-lower alkyl, acylamino-lower alkyl, (N-lower alkyl-piperazino or N-aryl- lower alkylpiperazino)-lower alkyl, or (morpholino, thiomorpholino, piperidino, pyrrolidino, piperidyl or N-lower alkylpiperidyl)-lower alkyl;

R_3 represents aryl that may be unsubstituted or substituted by R_4 and R_5;

R_4 or R_5 represents independently hydrogen, lower alkyl, lower alkoxy, halogen, hydroxy, acyloxy, lower alkoxy-lower alkoxy, trifluromethyl or cyano, oxy-C2-C3-alkylene, 1- or 2-napthyl; or R_4 and R_5 together on adjacent carbon atoms represent lower alkylenedioxy;

n represents an integer from 1 to 5;



Formula III

Wherein

R_6 is C_{3-12} alkyl, C_{3-12} alkenyl, C_{3-7}(optionally hydroxy-, C_{1-6} alkoxy-, amino-, or C_{1-6} alkylamino- substituted) cycloalkyl, C_{5-14} aryl, or C_{5-14} aryl(C_{1-6} alkyl), wherein aryl groups are optionally substituted by hydroxy-, C_{1-6} alkyl-, C_{1-6} alkoxy-, amino-, halo- or cyano-;

R_7 is C_{1-10} (optionally hydroxy- or C_{1-6}alkoxy- amino-, C_{1-6} alkylamino-, thiol-, C_{1-6} alkylmercapto- or protected hydroxy-, amino- or thiol- substituted) alkyl, C_{6-14} (optionally hydroxy-, C_{6-14}aryloxy-, or C_{1-6}alkoxy-, amino-, C_{1-6} alkylamino-, halo-, or cyano-substituted)aryl, or indolylmethyl;

R_8 is methyl, pyridyl, or a substituent of formula X-Y- wherein X is morpholino, pyridyl or aryl, and Y is C_{1-12}alkylene in which up to four of the methylene ($-CH_2-$) units are optionally replaced with -CO-, -NH-, $-SO_2-$ or -O-;

R_1 is hydrogen, lower alkyl, aryl, aryl-lower alkyl, mono- or poly-halo-lower alkyl, cycloalkyl, cycloalkyl-lower alkyl, cycloalkyl-cycloalkyl, aryl-lower alkyl-lower cycloalkyl, lower alkyl-cycloalkyl, lower alkoxy-lower alkyl-cycloalkyl, aryl-cycloalkyl, cycloalkyl-lower alkyl-cycloalkyl, halo-lower alkyl-cycloalkyl, hydroxy-lower alkyl, acyloxy-lower alkyl, lower alkoxy-lower alkyl, aryl-lower alkoxy-lower alkyl, lower alkyl-(thio, sulfinyl or sulfonyl)-lower alkyl, (amino, mono- or di-lower alkylamino)-lower alkyl, (N-lower alkyl-piperazino or N-aryl-lower alkylpiperazino)-lower alkyl, (morpholono, thiomorpholino, piperidino, pyrrolidino, piperidyl or N-lower alkylpiperidyl)-lower alkyl, acylamino-lower alkyl, piperidyl, N-lower alkylpiperidyl or a substituent of formula IV

$D-(O-(CR_9H)_z)_m-O-CH_2-$ Formula IV

wherein

z is 1, 2, 3 or 4;

m is 0, 1, 2 or 3;

each R_9 is

independently H, C_{1-10} (optionally hydroxy-, C_{1-6} alkoxy-, amino-, C_{1-6} alkylamino-, thiol-, C_{1-6} alkylmercapto- or protected hydroxy, amino or thiol substituted) alkyl, C_{2-6} alkenyl, C_{6-14}(optionally hydroxy-, C_{1-6} alkoxy-, amino-, C_{1-6} alkylamino-, halo- or cyano-substituted) aryl, or C_{6-14} (aryl) C_{1-6}alkyl;

D is hydrogen, C_{1-10} alkyl, C_{6-14} aryl, C_{6-14} aryl(C_{1-6} alkyl), (C_{6-14} aryl)carbonyl, or (C_{1-10} alkyl)carbonyl;

R_2 is hydrogen or lower alkyl,

(ii) or wherein

R (of formula II under (a)) and R_1 together with the chain to which they are attached from a 1,2,3,4-tetrahydro-isoquinoline, piperidine, oxazolidine, thiazolidine or pyrrolidine ring, each unsubstituted or substituted by lower alkyl; and

R_3 and R_2 have meaning as defined under (i);

(iii) or wherein

R_1 and R_2 together with the carbon atom to which they are attached form a ring system selected from lowercycloalkane which is unsubstituted or substituted by lower alkyl' oxa-cyclohexane, thia-cyclohexane, indane, tetralin, piperidine or piperidine substituted on nitrogen by acyl, lower alkyl, aryl-lower alkyl, (carboxy, esterified or amidated carboxy)-lower alkyl or by lower alkylsulfonyl; and

R_3 and R meaning as defined under (i);

or a pharmaceutically acceptable prodrug derivative thereof; or a pharmaceutically acceptable salt thereof.

3. Use of a matrix metalloproteinase inhibitor (or pharmaceutically acceptable salt or prodrug ester thereof) for the preparation of a medicament, for use in combination with heat shock and cytotoxic therapy for the treatment of tumor.

4. Use of a matrix metalloproteinase inhibitor (or pharmaceutically acceptable salt or prodrug ester thereof) in combination with heat shock and cytotoxic therapy for the treatment of tumor.

5. A package comprising a matrix metalloproteinase inhibitor (or pharmaceutically acceptable salt or prodrug ester thereof) together with instructions for use in combination with heat shock and cytotoxic therapy in the treatment of tumor.

6. A method according to claim 1, in which the matrix metalloproteinase inhibitor is a compound on formula I as defined in claim 2, or a pharmaceutically acceptable prodrug derivative thereof, or a pharmaceutically acceptable salt thereof.

7. A method according to claim 1, in which the matrix metalloproteinase inhibitor is one of the compounds disclosed in published international patent applications Nos. WO 98/14424, WO 97/22587 and EP 606046, or a pharmaceutically acceptable prodrug derivative thereof, or a pharmaceutically acceptable salt thereof.

8. A method according to claim 1, in which the matrix metalloproteinase inhibitor is N-hydroxy-2(R)-[[4-methoxyphenylsulfonyl](3-picolyl) amino] -3-methyl –butaneamide

hydrochloride) monohydrate, or a pharmaceutically acceptable prodrug derivative thereof, or a pharmaceutically acceptable salt thereof.

9. A method according to claim 1 in which the matrix metalloproteinase inhibitor, or a pharmacologically acceptable salt or prodrug ester, is in the form of a enteral composition.

10. All new methods, compositions and uses as hereinbefore described with reference to the examples.